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(54) **18-MEMBERED MACROCYCLES AND ANALOGS THEREOF**

FOREIGN PATENT DOCUMENTS

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WO	WO 96035702	11/1996
WO	98/002447	1/1998
WO	WO 2004/014295	2/2004
WO	WO 2005/112990	12/2005
WO	WO 2006/085838	8/2006
WO	07/048059	4/2007
WO	08/091518	7/2008
WO	08/091554	7/2008
WO	09/070779	6/2009

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(51) **Int. Cl.**

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(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,978,211	A	8/1976	Coronelli et al.
4,918,174	A	4/1990	Mc Alpine et al.
5,583,115	A	12/1996	Mc Alpine et al.
5,767,096	A	6/1998	Hochlowski et al.
7,378,508	B2	5/2008	Chiu et al.
7,507,564	B2*	3/2009	Shue et al. 435/180
2006/0257981	A1	11/2006	Shue et al.
2007/0105791	A1	5/2007	Sears et al.
2007/0173462	A1	7/2007	Shue et al.
2007/0259949	A1	11/2007	Chiu et al.
2008/0194497	A1	8/2008	Chiu et al.
2008/0269145	A1	10/2008	Shue et al.
2009/0163428	A1	6/2009	Chiu et al.
2010/0010076	A1	1/2010	Chiu et al.
2010/0035833	A1	2/2010	Ichikawa et al.
2010/0081800	A1	4/2010	Chiu et al.

Wolff et al., *Burgers Medicinal Chemistry and Drug Discovery* (1994) Wiley-Interscience, Fifth Edition, vol. I: Principles and Practice, pp. 975-977.*

Caldwell, J. (2001) *Do single enantiomers have something special to offer? Human Psychopharmacology: Clinical and Experimental*, vol. 16, S67-S71.*

Miller, L., Orihuela, C., Fronek, R., Honda, D., Dapremont, O. (1999) *Chromatographic resolution of the enantiomers of a pharmaceutical intermediate from the milligram to the kilogram scale. Journal of Chromatography A*, vol. 849, p. 309-317.*

Ackerman et al., "In vitro activity of OPT-80 against *Clostridium difficile*," *Antimicrobial Agents and Chemotherapy*, 2004, 48(6), pp. 2280-2282.

Cavalleri et al. "Structure and biological activity of lipiarmycin B," *The Journal of Antibiotics*, 1988, 41(3), pp. 308-315.

Remington: *The Science and Practice of Pharmacy*, published 2000 by Lippincott Williams and Wilkins, pp. 802-803.

Cambridge Crystallographic Data Centre Deposition No. 100349, (2000), CCDC No. 114782.

Ansel, H.C., Allen, Jr., L.V., Popovich, N. G., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Lippincott Williams & Wilkins, pp. 23-26, 179-180 and 196 (1999).

Arnone et al. "Structure Elucidation of the Macrocyclic Antibiotic Lipiarmycin" *Journal of the Chemical Society, Perkin Transactions 1, Chemical Society*, 1353-1359 (1987).

Caira "Crystalline Polymorphism of Organic Compounds" *Topics in Current Chemistry* 198:163-208 (1998).

Finogold et al. "In vitro activities of OPT-80 and comparator drugs against intestinal bacteria" *Antimicrobial Agents and Chemotherapy* 48(12): 4898-4902 (2004).

Gerding et al. "Clostridium difficile-associated diarrhea and colitis" *Infection Control and Hospital Epidemiology* 16(8):459-477 (1995).

Morissette et al. "High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids" *Advanced Drug Delivery Reviews* 56(3):275-300 (2004).

(Continued)

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(57) **ABSTRACT**

The present invention relates generally to the 18-membered macrocyclic antimicrobial agents called Tiacumicins, specifically, OPT-80 (which is composed almost entirely of the R-Tiacumicin B), pharmaceutical compositions comprising OPT-80, and methods using OPT-80. In particular, this compound is a potent drug for the treatment of bacterial infections, specifically *C. difficile* infections.

6 Claims, 1 Drawing Sheet